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Convergent Route to β-Amino Acids and to β-Heteroarylethylamines: An Unexpected Vinylation Reaction

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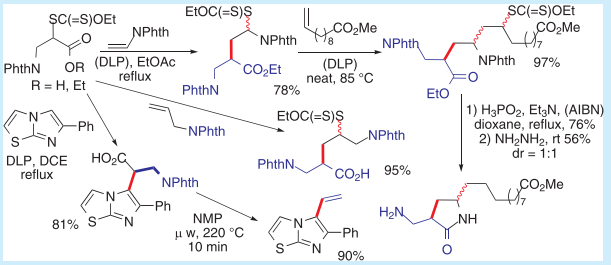
ABSTRACT: Various protected β^2-amino acids can be prepared by radical addition of β-phthalimido-α-xanthyl propionic acid, both as the free acid or as the ethyl ester. Successive radical additions provide access to more complex structures. In the case of the free acid, addition to certain heteroaromatics leads directly to β-heteroarylethylamines through spontaneous decarboxylation of the intermediate adduct. Forcing the decarboxylation in some cases generated a vinyl group by decarboxylative elimination of the phthalimido group.

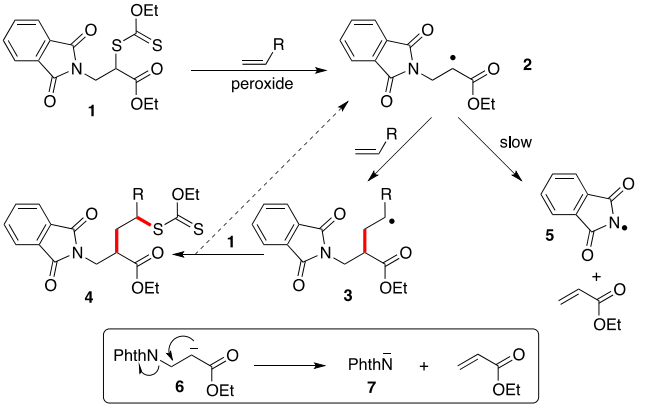


The β-amino acids and their derivatives are compounds of remarkable versatility.[1] They are precursors of β-lactams,[2] of metabolically stable peptidomimetics,[3] of various biologically active substances, and of numerous ligands for transition-metal-based catalysts.[4] The β-amino acid motif is present in a number of important natural products,[5] the most prominent of which are perhaps the anticancer taxol, the β-lactam family of antibiotics,[2] and β-lysine (or isolysine),[6] a mild antibiotic found in tears that causes lysis of many Gram-positive bacteria.

Most of the synthetic efforts have concerned β-amino acids with substituents on the carbon bearing the amino group,[1] the so-called β^3-amino acids according to the nomenclature introduced by Seebach.[7] β^2-Amino acids have attracted comparatively less attention, despite their potential utility for synthesis and for medicinal chemistry.[8] They are also much less readily accessible than their β^2 congeners. We describe now a convergent and flexible route to β^2-amino acids that exploits the lack of β-elimination of β-imido radicals and the unique properties of the degenerative xanthate addition-transfer process.[9,10] An offshoot of this study is a straightforward synthesis of β-heteroarylethylamines and an unexpected vinylation reaction.

The conception underlying our synthetic approach is outlined in Scheme 1. It hinges on the expectation that radical **2** derived from xanthate **1** will not undergo a β-elimination of phthalimidyl radical **5** before adding to the alkene. This is in contrast to the corresponding anion **6** which would readily eliminate phthalimidyl anion **7** (PhthN = phthalimido). A further non-negligible advantage of proceeding through radical intermediates generated from the corresponding xanthate is that nonactivated, electronically unbiased alkenes bearing numerous functionalities, especially polar groups, can be used as traps.[9]

Scheme 1. Radical-Based Route to β^2-Amino Acids



The synthesis of the requisite xanthate from known bromide **9**[11] was straightforward (Scheme 2). We were pleased to find that, as anticipated, the addition to allyl cyanide took place without β-scission of the phthalimide (DLP = dilauroyl peroxide, also sold under lauroyl peroxide, Laurox, or Luperox LP). The reaction was conducted *neat*, without any solvent, and furnished adduct **4a** in high yield. Other examples of addition are provided in the same Scheme. The yields are generally higher than typical xanthate additions and reflect presumably the increased electrophilic character of intermediate radical **2** caused by the presence of the adjacent

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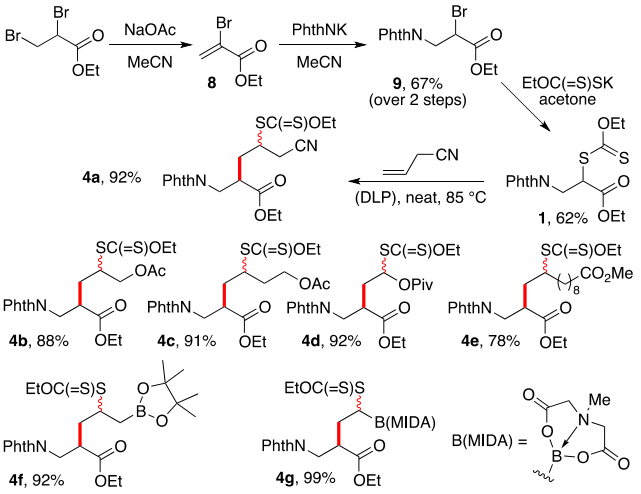
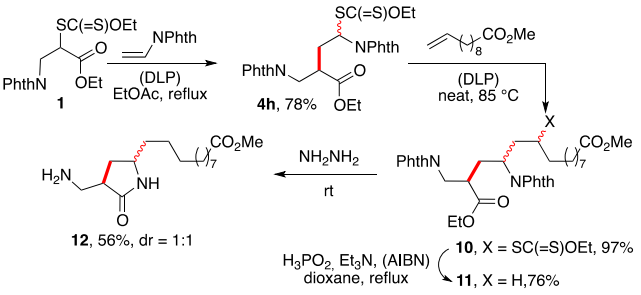
Scheme 2. Synthesis of Protected β^2-Amino Acids



phthalimide group. All the reactions were performed neat, except for the addition to vinyl MIDA boronate (example **4g**), which was performed in ethyl acetate at a 1 M concentration. In this case the yield was almost quantitative, reflecting the matched polarity between electrophilic radical **2** and electron-rich vinyl MIDA boronate. The boron substituent is negatively charged and releases electrons into the attached vinyl group.[12]

As can be seen upon inspection, many different functional groups are tolerated on the alkene. One interesting case is that of adduct **4d** to vinyl pivalate (Piv = pivalate). The carbon bearing both the xanthate and the pivalate has the oxidation level of an aldehyde, and such compounds have a very rich chemistry.[13] In all of these additions, a 1:1 mixture of diastereoisomers is produced. The xanthate group can be reductively removed, which simplifies the structures, or used to create another carbon−carbon bond and thus increase further the complexity. Both of these possibilities are illustrated in the sequence in Scheme 3.

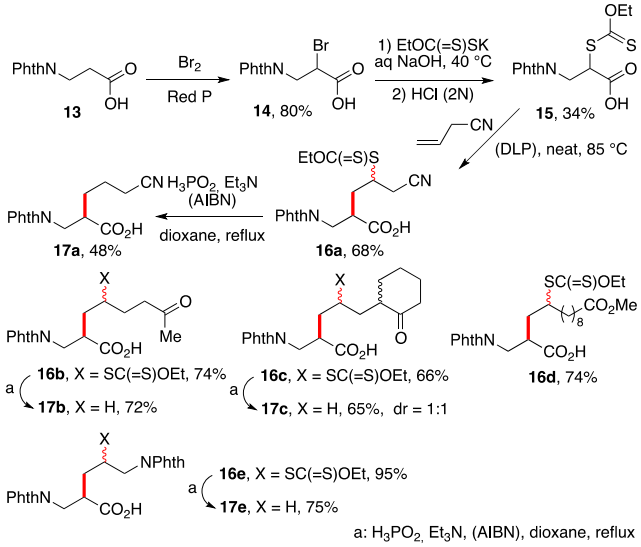
Scheme 3. Example of Successive Radical Additions



The addition of xanthate **1** to *N*-vinyl phthalimide was conducted in ethyl acetate at a 1 M concentration (Scheme 3). The resulting adduct **4h** could, in turn, be made to add to methyl 10-undecylenate to give a second adduct **10**, also in high yield. We had found previously that xanthates geminal to imide groups were suitable partners for the radical addition and provide a very powerful route to functional amines.[14] Indeed, this property was exploited to access β^3-amino acids.[15] Reductive elimination of the xanthate group using Barton's reagent[16] and deprotection of the phthalimide furnished aminomethyl substituted lactam **12**, where the ring closure occurred spontaneously. The ability to accomplish successive intermolecular additions is a unique property of the xanthate addition-transfer and allows rapid access to complex structures that would be very tedious to obtain by more conventional ionic or organometallic methods.

We further found that the radical additions could be accomplished from the free carboxylic acid **15** (Scheme 4).

Scheme 4. Synthesis of N-Protected β^2-Amino Acids



This compound was prepared from bromide **14**, itself obtained from 2-phthalimidopropionic acid **13** by the classical Hell−Volhard−Zelinsky reaction.[11,17] The substitution leading to xanthate **15** was surprisingly only modestly efficient, and more work is still needed to improve the yield. Nevertheless, the precursors are readily available, and sufficient quantities could be easily secured to complete the present preliminary study. The radical addition proceeded normally, even if the yields of adducts **16a−d** were generally slightly lower than with the corresponding ester **1** (Scheme 4). The xanthate was reductively removed in the first three products to give the simpler derivatives **17a−c**. The possibility of creating carbon−carbon bonds starting with a *free carboxylic acid* is remarkable, and a hallmark of radical processes, even if it has been seldom used hitherto. Only a handful of intermolecular additions to unactivated alkenes have been reported starting with iodoacetic and 2-iodopropionic acids.[18] In view of the numerous α-xanthyl carboxylic acids that can in principle be made by exploiting the Hell−Volhard−Zelinsky reaction and other processes, such as the radical addition of a xanthate to acrylic acid, this addition acquires a significant synthetic relevance.

Another interesting application of xanthate **15** is the direct introduction of an ethylamine moiety into heteroaromatics. β-(Hetero)arylethylamines represent perhaps the most important class of substances interacting with the central nervous system (CNS).[19] A few of these compounds are pictured in Figure 1. These can be endogenous neurotransmitters, such as dopamine **18** and serotonin **19**, or natural products with psychedelic and hallucinogenic activity, or even synthetic drugs such as the antidepressant venlafaxine and the antiobesity lorcaserine. The ethylamine motif highlighted in blue can be a simple pendant, substituted on the carbon chain or on the nitrogen, or even part of a ring.

The addition of xanthate **15** to a number of heteroaromatic structures could be accomplished by using stoichiometric

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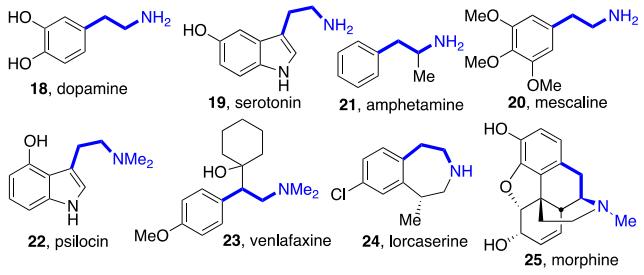
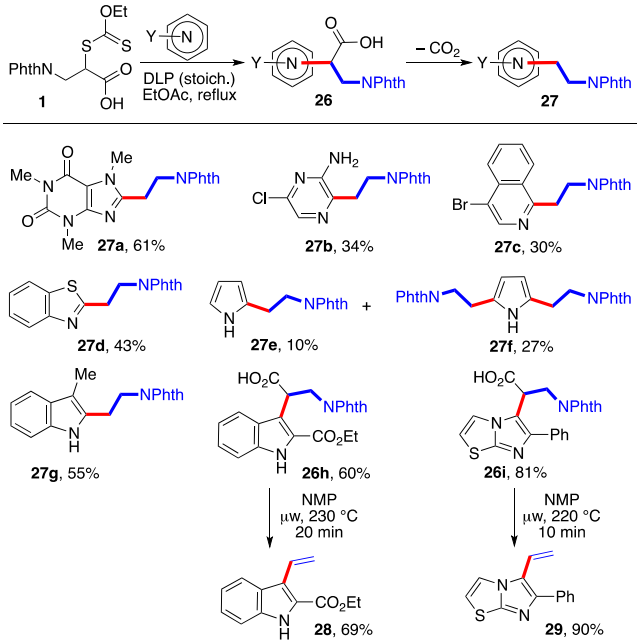


Figure 1. Examples of biologically active β-(hetero)arylethylamines.

amounts of peroxide.[20] The initial adduct **26** underwent spontaneous decarboxylation in some cases to furnish the corresponding phthalimide protected β-aminoethyl derivative (Scheme 5). This transformation is illustrated by the formation

Scheme 5. Synthesis of N-Protected Heteroarylethylamines

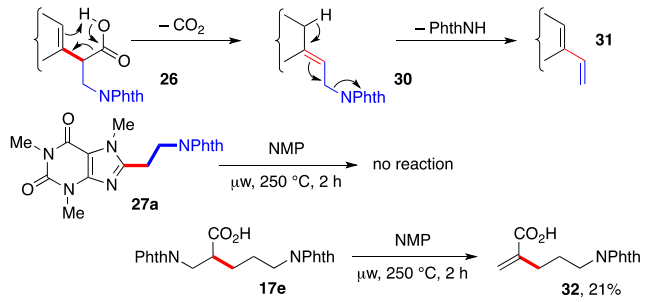


of compounds **27a–g** in moderate yield. Interestingly, the reaction with pyrrole gave rise to both the monoadduct **27e** and bis-adduct **27f**, the latter being the major product.

In contrast to the case of 3-methylindole (adduct **27g**), the reaction with ethyl 2-indolecarboxylate did not result in spontaneous decarboxylation, and carboxylic acid **26h** was isolated in 60% yield. Addition to 6-phenyl imidazo[2,1-*b*]thiazole also did not result in decarboxylation and furnished efficiently compound **26i**. Not only was the yield significantly higher than average, but the product crystallized directly from the reaction mixture and was isolated by simple filtration. This reaction was easily scaled up (1.2 g); albeit, the yield was somewhat lower (60%). Interestingly, when we attempted to decarboxylate both **26h** and **26i** by briefly heating a solution in *N*-methylpyrrolidone (NMP) in a microwave oven at 220–230 °C,[21] the reaction furnished cleanly vinyl derivatives **28** and **29**, respectively.

A possible explanation for the vinyl formation is provided in Scheme 6. At the high temperature required to decarboxylate adducts **26** which do not spontaneously extrude carbon dioxide, the retro-ene reaction leads to intermediate **30** which

Scheme 6. Possible Pathway for Vinyl Formation

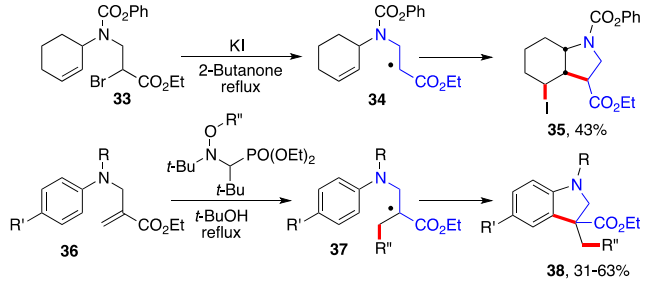


then eliminates phthalimide in a step that restores at the same time the aromaticity of the heteroaromatic ring. An attempt to accomplish just the decarboxylation step without concomitant elimination of the phthalimide by heating compound **26i** gradually was unsuccessful. Only vinyl derivative was observed forming at 170 °C. Indeed, the decarboxylation process is necessary for the elimination of the phthalimide. Prolonged microwave heating of caffeine derivative **27a** at the higher temperature of 250 °C did not result in any reaction. Furthermore, we found that, under these harsher conditions, aliphatic acid **17e**, which cannot undergo a retro-ene loss of CO_2, was converted in poor yield into acrylic acid product **32**.

The present expedient route to (hetero)arylmines complements the approach recently described by Jui and co-workers, where (hetero)arylmines were prepared by (hetero)aryl radical addition to enamides.[22]

It is further noteworthy that radical reactions have almost never been used for the synthesis of β^2-amino acids. Indeed, a literature search revealed reports by only two research groups, where a radical in position-2 of a β-amino acid or ester was generated and captured. In both cases, an *intra*molecular reaction is involved (**34** → **35** and **37** → **38** in Scheme 7).[23]

Scheme 7. Literature Examples of β^3-Amino Acid Esters Obtained by Radical Cyclization



Xanthates provide an opportunity for *inter*molecular additions, even to unactivated alkenes. This results in a versatile, modular, and flexible route to a broad variety of β^2-amino acids, thus considerably expanding the range of attainable structures. As stated in the introduction, β^2-amino acids are much less accessible than the more common β^3-amino acids. Furthermore, the same xanthate **15** serves to prepare β^2-amino acids and β-heteroarylethylamines, both of which are valuable for medicinal chemists. The cheapness and ready availability of the reagents, the mildness of the experimental conditions, and the compatibility with many functionalities, especially polar groups, are significant practical advantages.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01087.

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This article is dedicated with respect to the memory of Professors Dieter Enders (RWTH Aachen University) and Albert van Leusen (University of Groningen).

■ REFERENCES

(1) For reviews, see: (a) Juaristi, E., Ed. *Enantioselective Synthesis of β-Amino Acids*; Wiley: New York, 1997. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (c) Juaristi, E., Soloshonok, V., Eds. *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Wiley: Hoboken, NJ, 2005. (d) Kiss, L.; Fülöp, F. Synthesis of Carbocyclic and Heterocyclic β-Aminocarboxylic Acids. *Chem. Rev.* **2014**, *114*, 1116. (e) Fülöp, F.; Martinek, T. A.; Tóth, G. K. Application of alicyclic β-amino acids in peptide chemistry. *Chem. Soc. Rev.* **2006**, *35*, 323.

(2) (a) Page, M. I., Ed. *The Chemistry of β-Lactams*; Chapman and Hall: London, 1992. (b) Georg, G. I., Ed. *The Organic Chemistry of β-Lactams*; Verlag Chemie: New York, 1993.

(3) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aguilar, M.-I. β-Amino Acids: Versatile Peptidomimetics. *Curr. Med. Chem.* **2002**, *9*, 811.

(4) (a) Cabrele, C.; Martinek, T. A.; Reiser, O.; Berlicki, L. Peptides Containing β-Amino Acid Patterns: Challenges and Successes in Medicinal Chemistry. *J. Med. Chem.* **2014**, *57*, 9718. (b) Lamberth, C. Amino Acid Chemistry in Crop Protection. *Tetrahedron* **2010**, *66*, 7239.

(5) (a) Spiteller, P.; von Nussbaum, F. β-Amino Acids in Natural Products. In *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V., Eds.; Wiley: Hoboken, NJ, 2005; pp 19−91. (b) Shinagawa, S.; Kanamaru, T.; Harada, S.; Asai, M.; Okazaki, H. Chemistry of emeriamine and its analogs and their inhibitory activity in long-chain fatty acid oxidation. *J. Med. Chem.* **1987**, *30*, 1458−1463. (c) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. Total synthesis of 6-deoxy-6-aminoheptopyranuronic acid derivatives. *J. Org. Chem.* **1991**, *56*, 6523−6527.

(6) Frey, P. A. Travels with Carbon-Centered Radicals. 5′-Deoxyadenosine and 5′-Deoxyadenosine-5′-yl in Radical Enzymology. *Acc. Chem. Res.* **2014**, *47*, 540.

(7) (a) Hintermann, T.; Seebach, D. Synthesis of a β-Hexapeptide from (R)-2-Aminomethyl-alkanoic Acids and Structural Investigations. *Synlett* **1997**, *1997*, 437. (b) Seebach, D.; Gademann, K.; Schreiber, J. V.; Matthews, J. L.; Hintermann, T.; Jaun, B.; Oberer, L.; Hommel, U.; Widmer, H. 'Mixed' β-Peptides: A Unique Helical Secondary Structure in Solution. Preliminary Communication. *Helv. Chim. Acta* **1997**, *80*, 2033.

(8) (a) Lelais, G.; Seebach, D. β^2-Amino Acids—Syntheses, Occurrence in Natural Products, and Components of β-Peptides. *Biopolymers* **2004**, *76*, 206. (b) Nagula, G.; Huber, V. J.; Lum, C.; Goodman, B. A. Synthesis of α-Substituted β-Amino Acids Using Pseudoephedrine as a Chiral Auxiliary. *Org. Lett.* **2000**, *2*, 3527.

(9) For reviews, see: (a) Quiclet-Sire, B.; Zard, S. Z. On the Strategic Impact of the Degenerative Transfer of Xanthates on Synthetic Planning. *Isr. J. Chem.* **2017**, *57*, 202. (b) Quiclet-Sire, B.; Zard, S. Z. Fun with Radicals: Some New Perspectives for Organic Synthesis. *Pure Appl. Chem.* **2010**, *83*, 519. (c) Quiclet-Sire, B.; Zard, S. Z. The Degenerative Radical Transfer of Xanthates and Related Derivatives: An Unusually Powerful Tool for the Creation of Carbon-Carbon Bonds. *Top Curr. Chem.* **2006**, *264*, 201.

(10) For an account of the discovery of this process, see: (a) Zard, S. Z. The Genesis of the Reversible Radical Addition-Fragmentation-Transfer of Thiocarbonylthio Derivatives from the Barton-McCombie Deoxygenation. A brief Account and some Mechanistic Observations. *Aust. J. Chem.* **2006**, *59*, 663 For a discussion of the mechanism, see:. (b) Zard, S. Z. Radical Alliances: Solutions and Opportunities for Organic Synthesis. *Helv. Chim. Acta* **2019**, *102*, No. e1900134. (c) Zard, S. Z. Some Intriguing Mechanistic Aspects of the Radical Chemistry of Xanthates. *J. Phys. Org. Chem.* **2012**, *25*, 953.

(11) Gabriel, S. Über einige synthetisch verwertbare Derivate des Glycins und seiner Homologen. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 2647.

(12) Quiclet-Sire, B.; Zard, S. Z. Radical Instability in Aid of Efficiency. A Powerful Route to Highly Functional MIDA Boronates. *J. Am. Chem. Soc.* **2015**, *137*, 6762.

(13) Quiclet-Sire, B.; Zard, S. Z. Xanthates and Vinyl Esters, a Remarkably Powerful Alliance. *Heterocycles* **2019**, *99*, 742.

(14) For a review, see: Quiclet-Sire, B.; Zard, S. Z. The Xanthate Route to Amines, Anilines, and other Nitrogen Compounds. A Brief Account. *Synlett* **2016**, *27*, 680.

(15) (a) Han, S.; Jones, R. A.; Quiclet-Sire, B.; Zard, S. Z. A Convergent Route to Functional Protected Amines, Diamines, and β-Aminoacids. *Tetrahedron* **2014**, *70*, 7192. For a review on the application of xanthates to the synthesis of amino acids, see: (b) Zard, S. Z. The xanthate Route to Amino Acids. *Chimia* **2020**, *74*, 9.

(16) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. Radical Deoxygenations and Dehalogenations with dialkyl Phosphites as Hydrogen Atom Sources. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. On the Reduction of S-Alkyl-thionocarbonates (Xanthates) with Phosphorus Compounds. *Org. Lett.* **2003**, *5*, 1645.

(17) (a) Sonntag, N. O. The Reactions of Aliphatic Acid chlorides. *Chem. Rev.* **1953**, *52*, 237. (b) Watson, H. B. The Reactions of Halogens with Compounds Containing the Carbonyl Group. *Chem. Rev.* **1930**, *7*, 173.

(18) (a) Basante-Avendaño, A.; Guerra-Ayala, V. E.; Sánchez-Eleuterio, A.; Cordero-Vargas, A. A Free-Radical and Protecting-Group-Free Approach to (−)-Boschnialactone and γ-Lycorane. *Synthesis* **2019**, *51*, 2207. (b) Voutyritsa, E.; Triandafillidi, I.; Tzouras, N. V.; Nikitas, N. F.; Pefkianakis, E. K.; Vougioukalakis, G. C.; Kokotos, C. G. Photocatalytic Atom Transfer Radical Addition to Olefins Utilizing Novel Photocatalysts. *Molecules* **2019**, *24*, 1644. (c) Triandafillidi, I.; Kokotou, M. G.; Kokotos, C. G. Photocatalytic Synthesis of γ-Lactones from Alkenes: High-Resolution Mass Spectrometry as a Tool to Study Photoredox Reactions. *Org. Lett.* **2018**, *20*, 36. (d) Leon-Rayo, D. F.; Morales-Chamorro, M.; Cordero-Vargas, A. A Formal Intermolecular Iodolactonization Reaction Based

on a Radical-Ionic Sequence. *Eur. J. Org. Chem.* **2016**, *2016*, 1739. (e) Yu, H.; Li, C. Self-Protection: The Advantage of Radical Oligomeric Mixtures in Organic Synthesis. *J. Org. Chem.* **2004**, *69*, 142. (f) Cao, L.; Li, C. p-$MeOC_6H_4N_2$+BF_4-/TiCl3: a novel initiator for halogen atom-transfer radical reactions in aqueous media. *Tetrahedron Lett.* **2008**, *49*, 7380. (g) Byers, J. H.; Duff, M. P.; Woo, G. W. A one-step radical synthesis of pyrrol-2-acetic acids. *Tetrahedron Lett.* **2003**, *44*, 6853. (h) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. Radical Addition of 2-Iodoalkanamide or 2-Iodoalkanoic Acid to Alkenes with a Water-Soluble Radical Initiator in Aqueous Media: Facile Synthesis of γ-Lactones. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1963. (i) Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. Radical Addition of 2−1odoalkanamide or 2−1odoalkanoic Acid to Alkenols Using a Water-Soluble Radical Initiator in Water. A Facile Synthesis of γ-Lactones. *Tetrahedron Lett.* **1999**, *40*, 519. (j) Foubelo, F.; Lloret, F.; Yus, M. Enolic Radical Derived from Acetic Acid: A Useful Radical Alternative to Acetate Enolate in Michael-Type Reactions. *Tetrahedron* **1993**, *49*, 8465.

(19) Glennon, R. A. The 2014 Philip S. Portoghese Medicinal Chemistry Lectureship: The "Phenylalkylaminome" with a Focus on Selected Drugs of Abuse. *J. Med. Chem.* **2017**, *60*, 2605.

(20) El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. A Unified Access to Diverse Heteroaromatic Scaffolds Using the Radical Chemistry of Xanthates. *Org. Biomol. Chem.* **2012**, *10*, 5707 and references cited therein..

(21) Huang, Q.; Zard, S. Z. An Inexpensive Radical Methylation and Related Alkylations of Heteroarenes. *Org. Lett.* **2018**, *20*, 1413.

(22) Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Zihao Xu, Z.; Jui, N. T. A Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019**, *141*, 4147.

(23) (a) Mori, M.; Kubo, Y.; Ban, Y. Atom Transfer Cyclization of α-Halonitrile and α-Halocarbonyl Compounds. *Heterocycles* **1990**, *31*, 433. (b) Mori, M.; Kubo, Y.; Ban, Y. Palladium Catalyzed Ene-Halogenocyclization of α-Haloester Having Internal Double Bond with the Low-Valent Metal Complex. *Tetrahedron* **1988**, *44*, 4321. (c) Mori, M.; Kubo, Y.; Ban, Y. Reaction α-Haloester Having Internal Double Bond with the Low-Valent Metal Complex. *Tetrahedron Lett.* **1985**, *26*, 1519. (d) Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Guerret, O.; Ciufolini, M. A. Alkoxyamine-Mediated Radical Synthesis of Indolinones and Indolines. *Org. Lett.* **2003**, *5*, 4943.

https://dx.doi.org/10.1021/acs.orglett.0c01087
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